Noninvasive Brain Stimulation for the Study of Memory Enhancement in Aging

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Abstract. Noninvasive brain stimulation (NIBS) techniques such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) have recently attracted interest due to their potential for transiently improving cognitive functions and memory in human beings. In aging, these techniques may prove particularly valuable given the impact of age-related cognitive dysfunction on quality of life. The present review summarizes the currently available evidence of working and episodic memory enhancement achieved using NIBS in healthy elderly people. The evidence reviewed indicates that research is still at an early stage and that there is a need to define the best procedures for operating and performing multicenter characterization of protocols. However, a limited number of sham-controlled studies have reported improvements in both working memory and episodic memory domains among healthy elders using NIBS. Furthermore, some studies have demonstrated the long-term persistence of the positive effects, a finding that opens up the possibility of using NIBS as an adjuvant therapeutic strategy in the management of age-associated memory decline. However, the relevance of many of the variables involved and approaches used remains to be elucidated, including the potential benefits of single versus multiple NIBS sessions, the putative synergistic effects of using NIBS in combination with cognitive training, and the importance of individual differences between subjects. Overall, NIBS techniques represent a promising opportunity for psychologists seeking strategies to improve memory functions in the elderly. Nevertheless, their use requires appropriate technical knowledge coupled with a clear understanding of the neurophysiology and cognitive neuroscience of aging. Only by ensuring that these requirements are met can we refine our hypotheses and select the best procedures for optimizing the effect of NIBS on cognition.

Keywords: aging, memory, improvement, noninvasive brain stimulation

In developed countries, the size of the elderly population is growing rapidly. By 2050, the elderly in these regions are expected to outnumber children by two to one (United Nations, 2013). This substantial increase is due to advances in medicine, public health measures, and rising standards of living (Cohen, 2003). While maturity provides experience and knowledge, aging also entails cognitive and motor decline and is a significant risk factor for several neurodegenerative disorders, especially Alzheimer's disease (AD; Hebert, Scherr, Bienias, Bennett, & Evans, 2003). Cognitive dysfunction is one of the conditions that negatively impact quality of life in the elderly (Plassman et al., 2008); it is therefore vital to study and develop programs to maintain cognitive function and independence.

There is accumulating knowledge about how cognition changes with age. Many aspects of information processing become less efficient (Craik & Salthouse, 2007), a phenomenon which, on a population basis, is particularly marked from the seventh decade of life onwards (Rönnlund, Nyberg, Bäckman, & Nilsson, 2005). Reduced cognitive performance associated with aging is not a homogeneous process; certain functions show substantial decline, while others remain stable throughout the lifetime. Among the cognitive abilities affected by aging, working and episodic memory are perhaps the ones that stand out the most. There is strong evidence that working memory (WM), the process by which information is held and manipulated for very short time intervals, decreases with age (Reuter-Lorenz &

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Sylvester, 2005) and is partially responsible for losses in long-term memory. Long-term episodic memory refers to the explicit recollection of events and is also reported to be highly susceptible to age (Zacks, Hasher, & Li, 2000). Vulnerability with advancing age has been demonstrated for the different subprocesses of long-term episodic memory, such as the encoding, storage, and retrieval of information.

Memory dysfunctions in the elderly are accompanied by age-related changes in the brain systems that support these cognitive functions. Neuroimaging has revealed that aging in the human brain is characterized by gray matter cortical thinning and loss of volume (Fjell et al., 2009; Good et al., 2001), ventricular expansion (Earnest, Heaton, Wilkinson, & Manke, 1979), decreased density of white matter fibers (Sala et al., 2012), neurotransmitter depletion (Reeves, Bench, & Howard, 2002), and alteration of functional brain networks (Ferreira & Busatto, 2013; Spreng, Wojtowicz, & Grady, 2010). However, age-related changes are not homogeneous, since some regions show steeper declines than others. Specifically, fronto-parietal executive networks, including the dorsolateral prefrontal cortex (PFC) and the superior parietal lobe, which both play a fundamental role in WM processes, are among the regions that suffer the greatest age-related changes (Good et al., 2001). Similarly, the medial temporal lobe is particularly affected by the deleterious effects of age (Fjell, Westlye, et al., 2014; Fjell et al., 2013). Coupled with the PFC, this system includes the hippocampus, the entorhinal cortex, and the parahippocampal cortex and plays an essential role in several phases of long-term episodic memory. As well as encoding, storing, and recalling information, episodic memory includes other processes such as reconsolidation, which involves the reactivation of consolidated memories (usually through a reminder) to a labile state in which these memories can be modified before they restabilize (Schwabe, Nader, & Pruessner, 2014). Finally, the default mode network (DMN) is a set of brain regions which fluctuates synchronically when subjects are at rest and is deactivated during goal-oriented activity. The DMN comprises the prefrontal and posteromedial areas as well as temporal middle and medial areas, and is essential for memory functions. It is particularly vulnerable to the effects of advanced age, in which a progressive reduction in functional connectivity is observed between the main anterior and posteromedial cortical nodes (Andrews-Hanna et al., 2007; Vidal-Piñeiro, Valls-Pedret, et al., 2014) as well as with the hippocampal formation (Salami, Pudas, & Nyberg, 2014). This susceptibility may be related to the network's central role as a system that subtends lifelong brain plasticity adaptations (Fjell, McEvoy, et al., 2014; Fjell et al., 2009).

In summary, memory processing dysfunction is a common, important phenomenon in the elderly and has significant implications for health and for society as a whole. One suitable approach to help to counteract age-related cognitive impairment is the use of cognitive training, which focuses on improving specific cognitive functions through intensive practice of cognitive exercises. Cognitive training is restorative in nature, aiming to reinstate reserve brain capacities or to provide greater resilience against neuropathology (Gates & Sachdev, 2014). Although randomized clinical trials are still scarce, meta-analyses and literature reviews indicate that cognitive training can significantly enhance cognitive function in healthy elders in terms of episodic memory, working memory (WM), executive functions (EFs), and processing speed (Gates, Fiatarone Singh, Sachdev, & Valenzuela, 2013; Kelly et al., 2014).

The present review focuses on an additional approach which has recently been proposed for enhancing cognitive functions in aging: the use of noninvasive brain stimulation (NIBS) techniques. NIBS is able to obtain potential cognitive benefits in aging as it allows the external induction or modulation of plasticity-enhancing mechanisms. Therefore, it may well be a valid option for tackling age-related cognitive decline (Elder & Taylor, 2014; Gutchess, 2014), either alone or in combination with other tools that aim to enhance adaptive plasticity responses such as cognitive training (Bentwich et al., 2011; Park, Seo, Kim, & Ko, 2014) or physical interventions (Prakash, Voss, Erickson, & Kramer, 2015). Applied in the elderly population, these procedures may help to optimize the usage of preserved functional brain resources that are linked to the maintenance of cognitive performance (Nyberg, Lövdén, Riklund, Lindenberger, & Bäckman, 2012) or may engage compensatory mechanisms (Cabeza, Anderson, Locantore, & McIntosh, 2002) which can moderate impending age-related or pathology-related brain changes (Bartrés-Faz & Arenaza-Urquijo, 2011).

The present review summarizes the available evidence on working and declarative learning/memory enhancements reported with the use of NIBS in healthy elderly individuals (i.e., those without diagnoses of neuropsychiatric conditions). Previous studies have reported improvements in older adults with depression (Moser et al., 2002), in neuro-rehabilitation following stroke, and in neuropsychiatric or neurological conditions (Elder & Taylor, 2014; Flöel, 2014; Kuo, Paulus, & Nitsche, 2014). Findings involving the effects of NIBS on other cognitive domains in healthy older adults, such as language generation (Meinzer, Lindenberg, Antonenko, Flaisch, & Flöel, 2013; Meinzer, Lindenberg, Phan, et al., 2014), naming (Cotelli et al., 2010; Fertonani, Brambilla, Cotelli, & Miniussi, 2014; Ross, McCoy, Coslett, Olson, & Wolk, 2011), inhibitory responses (Harty et al., 2014), and motor learning (Zimerman et al., 2013), are not directly addressed in this review, but references are included when appropriate.

Before focusing on the specific studies in this field, a general introduction to the relevant aspects of NIBS is provided. A thorough review of these techniques is beyond the scope of this manuscript, and readers are referred to several excellent articles already published on this topic (Dayan, Censor, Buch, Sandrini, & Cohen, 2013; Hallett, 2007; Stagg & Nitsche, 2011) including the ones published in this issue.

Briefly, the NIBS techniques most commonly used in memory studies with older adults are transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). Other techniques such as transcranial alternating and random noise stimulation (tACS; tRNS) are also widely reported in the neuroscience literature. TMS can be applied either using single pulses or in a repetitive fashion (repetitive TMS, rTMS) and is based on the principles of electromagnetic induction. A strong and short electric pulse of current passes through a coil placed over the person's head, inducing a brief changing magnetic field. This in turn causes a secondary electric current in a nearby conducting tissue such as the brain. The effects of the secondary electrical currents can be sufficient to depolarize cortical neurons. The final outcome depends on the characteristics of the stimulation as well as on the functional properties of the targeted area (i.e., degree of activity) when stimulated. In contrast, tDCS uses constant low currents delivered to specific brain areas through a pair of electrodes. This has a neuromodulatory effect, possibly modifying membrane polarization and therefore the neuron firing threshold potential, and changing the cortical excitability in the targeted brain areas (Nitsche & Paulus, 2000).

While the effects of NIBS depend on several parameters, it is generally accepted that high-frequency stimulation by TMS ($\geq$ 5 Hz) and anodal tDCS increase cortical excitability, whereas low-frequency stimulation by TMS ($\leq$ 1 Hz) and cathodal tDCS leads to cortical inhibition. Additionally, NIBS may produce brain changes in distant but functionally related regions, affecting the activity not only of discrete areas but also of entire brain networks (Bortoletto, Veniero, Thut, & Miniussi, 2015).

Critically for cognitive neuro-enhancement, the effects of both tDCS and rTMS can persist after stimulation cessation – the so-called "after effects." These are considered residual functional brain responses which can last for relatively prolonged periods and are thought to be mediated through the modulation of brain plasticity mechanisms related to long-term potentiation (LPT) and long-term depression-like (LTD) phenomena (Liebetanz, Nitsche, Tergau, & Paulus, 2002; Nitsche et al., 2003). However, it should be noted that it is still not clear how putative LTP/LTD-like effects induced by NIBS correspond to the changes in brain activity or connectivity observed using functional neuroimaging techniques.

Methods, Search Criteria, and Studies Included

Our search was performed using the PubMed database. We included studies available online up to December 15, 2014. The search used the following NIBS keywords: "Transcranial Magnetic Stimulation or TMS," "theta-burst stimulation," "transcranial direct current stimulation or tDCS," "transcranial alternating current stimulation or tACS," and "transcranial random noise stimulation or tRNS." Further, we combined these with a term referencing elderly subjects: "aging," "ageing," "old adults," "older adults," and "elderly." We reviewed the titles and abstracts from the resulting searches and selected those that referred to cognitive studies. Those that looked at cognitive enhancements associated with NIBS administration were reviewed in full.

We excluded review reports and studies performed in samples where the age of participants was under 40 years. We also excluded studies of patients and of non-human subjects. Finally, the main review included investigations reporting or hypothesizing changes in brain function or activity associated with NIBS in working and episodic memory functions in the elderly. We identified eight articles that met the review criteria, and these are summarized in Table 1. A brief description of the main findings as well as the interpretation of the observed effects is provided in the next section.

Review of the Use of NIBS Neuro-Enhancement Protocols in the Healthy Elderly

In what we believe to have been the first published study aiming to improve declarative memory processes in non-demented older individuals (Solé-Padullés et al., 2006) used high-frequency repetitive TMS (rTMS; 5 Hz) over the PFC in a group of participants with subjective cognitive complaints. This investigation included a sham-controlled design with the administration of *offline* rTMS in the interval between two equivalent face-name associative learning tasks. Increased recognition memory performance was observed only after real stimulation. Further analyses of brain activity by functional magnetic resonance imaging (fMRI) were performed during the encoding task and evidenced greater bilateral prefrontal patterns of brain activity in the group that received real stimulation. Particularly during the baseline (pre-stimulation) encoding task, PFC activity was dominated by left-sided engagement during learning. In contrast, in the second equivalent fMRI session after TMS, areas of the right PFC became more activated.

An unusual feature of this study, which may have influenced the results, was the use of a double-cone coil This device is known to be less focal than the more frequently employed figure-of-eight coil which allows dual hemisphere stimulation when positioned over the superior PFC. Therefore, the cognitive improvements observed were interpreted as evidence that rTMS could have intensified the expression of latent compensatory mechanisms by increasing the bilateral recruitment of the frontal cortex. This finding was consistent with the cognitive neuroscience models of aging (Cabeza, 2002). More specifically, the results were also consistent with classical fMRI observations (Cabeza et al., 2002; Reuter-Lorenz et al., 2000) and "causal mapping" *r*TMS studies. After altering brain activity through online rTMS (Bestmann et al., 2008; Rossi et al., 2004), the presence of a compensatory process was reported in the right hemisphere, while another study (Manenti, Brambilla, Petesi, Miniussi, & Cotelli, 2013) found that elderly with high cognitive performance relied more on the functional integrity of the right PFC when faced with cognitive demands.

In a further report, data from the active stimulation group of the study mentioned above (Solé-Padullés et al., 2006)

Table 1. Summary of studies using NIBS neuro-enhancement protocols on memory function in elders

Study	Sample	Stimulation type	Stimulation design & parameters	Stimulation site & parameters	Function	Task	Main result	Other results
Repetitive transcranial magnetic stimulation studies								
Solé-Padullés et al., Cerebral Cortex, 2006	40 OA (ma: 67). Memory complaints and low memory function.	Double-cone coil. Single-session stimulation. rTMS 5 Hz, 80% MT. 10 trains lasting 10 s each Total duration 5 min.	Sham-controlled study. Mixed design: Between group factor: real vs. sham TMS. Within group factor: memory performance and fMRI activation before vs. after TMS.	Prefrontal cortex. Offline stimulation.	Visual associative (episodic) memory.	Face-name learning task.	Recognition memory improvement following real TMS.	Increased brain activity in frontal and parietooccipital areas as measured by fMRI in the real TMS group.
Peña-Gómez et al., PLoS One, 2012	20 OA (ma: 67) pertaining to the active TMS group of the Solé-Padullés et al. (2006) study.	Double-cone coil. Single-session stimulation. rTMS 5 Hz, 80% MT. 10 trains lasting 10 s each Total duration 5 min.	Only real rTMS. Mixed design: Between group factor: presence or absence of ApoE ε4 allele. Within group factor: memory performance and fMRI activation before vs. after TMS.	Prefrontal cortex. Offline stimulation.	Visual associative (episodic) memory.	Face-name learning task.	Equivalent recognition memory improvement for both genetic groups.	After rTMS brain activity patterns of ApoE ε4 carriers show higher resemblance to those of non-ε4 carriers.
Vidal-Piñeiro et al., Brain Stimulation, 2014	24 OA (ma: 72).	Figure-of-eight coil. Single-session stimulation. Intermittent TBS, 80% AMT. Trains every 200 ms during 2 s repeated once every 10 s for a total of 20 repetitions. Total duration 3 min.	Sham-controlled study. Mixed design: Between group factor: iTBS vs. sham stimulation. Within group factor: memory performance and fMRI activation before vs. after TMS.	Left inferior frontal gyrus. Neuronavigated TMS. Offline stimulation.	Verbal encoding (words) task.	Perceptual vs. semantic encoding (level of processing).	No main TMS effects on accuracy or in reaction time on the memory task.	iTBS increased fMRI activation specifically under semantic processing in the stimulation site as well as distally in posterior occipital and cerebellar areas.
Transcranial direct current stimulation (tDCS) studies								
Flöel et al., Neurobiology of Aging, 2012	20 OA (ma: 62.1).	1 mA for 20 min.	Sham-controlled study. Crossover study, counterbalanced: all subjects underwent one sham and one real tDCS session a week apart.	Anodal electrode over right temporoparietal. Cathodal electrode over contralateral orbital. Online stimulation.	Visuospatial learning.	Object-location learning.	Delayed free recall (1 week) but not learning or immediate recall was significantly better after a tDCS compared to sham.	

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Table 1. (Continued)

Study	Sample	Stimulation type	Stimulation design & parameters	Stimulation site & parameters	Function	Task	Main result	Other results
Manenti et al., Frontiers in Aging Neuroscience, 2013	32 OA (ma: 67.9); 32 young (ma: 23.7)	1.5 mA for 6 min.	Sham-controlled study. Between group comparison, 4 groups: $N = 16$ OA and $N = 16$ young received sham or anodal ($N = 8$ in each group) stimulation over left/right DLPFC. $N = 16$ OA and $N = 16$ young received sham or anodal ($N = 8$ in each group) over left/right parietal.	Anodal electrode over left/right DLPFC or left right parietal. Cathodal electrode over the contralateral orbital. Online stimulation.	Verbal episodic memory encoding.	Presentation of abstract or concrete words to encode for latter recognition.	Compared to sham stimulation, faster RT amongst OA under left DLPFC or parietal tDCS. Faster RT for young subjects under both left and right DLPFC or parietal tDCS.	
Berryhill & Jones, Neuroscience Letters, 2013	25 OA (ma: 63.7)	1.5 mA for 10 min.	Sham-controlled study. Crossover: All subjects stimulated under three conditions: F3, F4, and sham in a counterbalanced order with a washout period of 24 h between sessions.	Anodal electrode (or sham) over F3 or F4, cathodal over contralateral check. Online stimulation.	Working memory.	Visual (symmetrical shapes) and verbal (consonants) WM tasks (2-back).	Only highly educated elders benefited from tDCS regardless of the hemisphere stimulated and the type of WM task.	
Park et al., Neuroreport, 2014	40 OA (ma: 69.7)	2 mA during 30 min per session, performed 5 times a week for 2 weeks.	Sham-controlled study. Between group comparison, real tDCS ($N = 20$) vs. sham ($N = 20$). Both groups receive computer-assisted cognitive training during stimulation.	Two tDCS stimulators are used. Anodal tDCS over F3 and F4 and cathode attached on the nondominant arm. Online stimulation.	Primary outcome: Working memory. Secondary outcomes: verbal memory, visual memory, attention, motor coordination.	Main task: Verbal WM (letters) 2-back task.	RT and accuracy improvement for the main task in the active tDCS group up to 28 days of completion of the training sessions.	Improvements only in the active tDCS group were also observed in an attentional task (digit span).

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Table 1. (Continued)

Study	Sample	Stimulation type	Stimulation design & parameters	Stimulation site & parameters	Function	Task	Main result	Other results
Sandrini et al., Frontiers in Aging Neuroscience, 2014	36 OA (ma: 67)	1.5 mA for 10 min.	Sham-controlled study. Between group comparison. Three groups (*N* = 12) receive tDCS during memory reconsolidation: 1 - Anodal tDCS in the same room as in Day 1. 2 - Sham tDCS in the same room as in Day 1. 3 - Anodal tDCS in a different room and without memory reactivation.	Anodal tDCS to F3 and cathodal to supraorbital. Online stimulation.	Verbal memory reconsolidation.	20 concrete words subject had to memorize on Day 1. Memory reconsolidation plus tDCS on Day 2 (24 hr latter) and memory recall on Day 3 (48 hr after learning session) and Day 30 (after 1 month).	Groups that received real tDCS during reconsolidation show reduced forgetting on Day 3 and Day 30.	No interaction between tDCS and reconsolidation memory effects.

Note. AMT: active motor threshold; atDCS: anodal tDCS; DLPFC: dorsolateral prefrontal cortex; F3: left frontal location according to the EEG 10-20 electrode positioning system; F4: right frontal location according to the EEG 10-20 electrode positioning system; fMRI: functional magnetic resonance imaging; Hz: hertz, ms: milliseconds; mA: miliampere; MT: motor threshold; OA: old adult, ma: mean age; RT: reaction times; rTMS: repetitive transcranial magnetic stimulation; TBS: theta-burst stimulation; tDCS: transcranial direct current stimulation; WM: working memory.

were reanalyzed to determine whether the main genetic risk factor for AD, the apolipoprotein E (APOE) ε4 allele, had any effect on brain responses to rTMS (Peña-Gomez et al., 2012). In this sub-analysis, relevant differences appeared at the level of the reorganization of brain networks following brain stimulation in genetic subgroups. Specifically, among the individuals at genetic risk for AD, rTMS resulted in a robust reorganization of brain networks expressed during effortful encoding phases, and affected the functional organization of the DMN regions (investigated as a set of areas showing deactivation during cognitive activity). The most striking observation after TMS was that, despite clearly dissimilar patterns at baseline, the brain network topography was now similar in the group with the genetic risk factor and in the group without it.

TMS thus normalized brain connectivity patterns in individuals at genetic risk for AD, a finding borne out by subsequent reports in patients with healthy aging (Meinzer et al., 2013) as well as in patients with mild cognitive impairment (MCI; Meinzer, Lindenberg, Phan, et al., 2014; Petersen, 2011). In these investigations, which focused on word generation tasks, anodal tDCS was able to attenuate the differences in brain activity and connectivity between the intervention and control groups, with few differences being observed between old and young adults or between MCI-affected and healthy older adults following stimulation.

Although some previous studies have reported memory improvements in the elderly, others have failed to show any behavioral changes in spite of observing brain activity and connectivity modulation in response to NIBS. This lack of a behavioral impact coupled with a physiological effect of TMS is acknowledged in the literature. Here, when stimulation modulates the remote physiological response in a state-dependent manner but does not disrupt performance it should not be regarded as a null result, as it permits the study of functional relationships between areas that vary under different conditions, while avoiding the complications of interpreting the neural changes in terms of behavioral modulation. Thus, this approach makes it possible to study how the different areas relate to and influence each other under different behavioral states (Feredoes, Heinen, Weiskopf, Ruff, & Driver, 2011). Alternatively, when stimulation is applied offline, changes in physiological correlate without behavioral changes can be interpreted as the engagement of compensatory mechanisms (Ruff et al., 2009).

Vidal-Piñeiro et al. (2014) aimed to improve episodic Q5 memory during a task that included two levels of encoding (semantic vs. perceptual encoding strategies). For this purpose, TMS was applied over the left inferior frontal gyrus and in the interval between two memory tasks performed within the fMRI. We used intermittent theta-burst stimulation (iTBS), a patterned TMS stimulation that usually leads to excitatory post-effects (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005). Unexpectedly, iTBS did not lead to memory modulations, but task-dependent modifications in memory networks were observed. Application of iTBS enhanced cortical activity, both locally and in distal connected visual regions, specifically during deep encoding trials. These findings were interpreted as evidence of a top-down circuit implicated in semantic-based encoding strategies which might be related to the observation of relatively preserved memory in aging when stimuli are semantically encoded (Logan, Sanders, Snyder, Morris, & Buckner, 2002).

In another study, facilitation of episodic memory was observed in elderly participants following NIBS (Manenti, Brambilla, Petesi, Ferrari, & Cotelli, 2013). Using tDCS, the authors reported that when the anodal electrode was positioned on the left dorsolateral PFC or on the parietal region, but not in the corresponding areas in the right hemisphere, participants exhibited improved reaction times during a verbal memory recognition task. In a young group, the beneficial effect was found for stimulation of both left and right dorsolateral PFC and the parietal region. The authors interpreted this as evidence of enhanced verbal coded strategies supported by the left hemisphere in the elderly, which improved performance in the system with loss of regional specialization. In contrast, both hemispheres appeared to contribute equally to performance outcomes in young subjects, the left with verbal strategies and the right with visuospatial processes. Therefore, this study linked the cognitive improvement induced by NIBS in old adults to theories of bi-hemispheric compensation and models of dedifferentiation of functional specificity with advancing age (Park & Reuter-Lorenz, 2009).

Sandrini and colleagues (2014) recently investigated the effects of tDCS on consolidated memories using a memory reconsolidation paradigm. The concept of reconsolidation highlights the fact that reactivation of consolidated memories through a cue forces the triggered memory into a transiently vulnerable state where it can be strengthened, disrupted, or updated for a short period (Alberini & Ledoux, 2013). Previous reports by the same group (Sandrini, Censor, Mishoe, & Cohen, 2013) using the same paradigm in young individuals showed that rTMS delivered to the DLPFC is able to induce long-lasting memory enhancements if applied during reconsolidation. In their study with elderly participants, 24 hr after the initial learning phase, the authors tested whether anodal tDCS on the left dorsolateral PFC could enhance the effects of reconsolidation of long-term memory performance. They showed that, compared with sham stimulation, active tDCS decreased the "forgetting rate" tested 48 hr and 1 month after the initial memory encoding. However, tDCS induced better long-term memory performance irrespective of whether the subjects underwent a period of memory reconsolidation in the form of a spatial contextual reminder. The ability to reinforce memories after acquisition raises the possibility that NIBS could be applied at different stages of the memory process, not only during external-oriented cognitive tasks. In addition, it might promote the use of NIBS as an adaptable memory enhancement tool when targeting daily routines.

The right temporoparietal region is known to be involved in object-location learning. Consequently, Flöel and colleagues (2012) applied tDCS to this area while subjects learnt to identify the position of picture buildings in two-dimensional street maps. The authors observed that learning and immediate recall were not affected by tDCS, but that the real stimulation created better long-term (1 week) memory performance compared with sham. The authors suggested that tDCS might have increased hippocampal activity during object-location learning, thereby improving memory performance. The studies of both Sandrini (Sandrini et al., 2014) and Flöel (Flöel et al., 2012) suggest that the effects of tDCS interact with consolidation processes, in accordance with other studies in the literature which report behavioral improvements. For instance, using a complex motor skill learning task over five consecutive days in young individuals, Reis and colleagues (2009) observed benefits induced by anodal tDCS but only when considering *offline* measures (i.e., improvements between training sessions, reflecting consolidation of the learning period). However, in the specific case of elders this proposal is challenged by the findings of (Zimerman et al., 2013) and the previous study by Hummel (Hummel et al., 2010) which measured the performance of a set of motor skill tasks and motor skill learning, respectively, and reported improvements during *online* motor skill acquisition. Similarly, using a confrontation-naming task, Fertonani and colleagues (2014) observed greater beneficial *online* effects for older individuals than for younger ones. Altogether, the findings may be compatible with the interpretation that in young individuals, the fine-tuning of the cerebral systems during task performance would rule out any additional improvement, whereas improvement might be possible in the case of elder participants with "suboptimal" cognitive processing during task performance (Zimerman et al., 2013).

Finally, two other studies focusing on the WM domain have used tDCS over the PFC cortex. (Berryhill & Jones, 2012) performed a sham-controlled experiment with anodal tDCS over the dorsolateral PFC (i.e., with the anodal electrode located in either F3 or F4 of the 10-20 EEG system) for 10 min prior to visuospatial and verbal WM tasks. They observed that tDCS improved WM performance on both tasks independently of the stimulation site (left or right PFC), but that this effect was only evident in individuals with high levels of education. The data were interpreted as evidence of the need for bilateral recruitment in order to obtain optimal cognitive performance in the elderly (Cabeza et al., 2002). Better educated individuals were more likely to recruit the PFC bilaterally, leading to better cognitive performance, a pattern that may have been facilitated by the electrode montage used. In the other report of WM, (Park et al., 2014) applied bilateral anodal prefrontal (F3, F4) tDCS during computer-assisted cognitive training. In a sham-controlled study, the authors observed greater improvements in verbal WM and in attention (digit span forward) under real tDCS than in sham stimulation. Notably, the cognitive benefits lasted for almost a month after stimulation.

Summary of the Use of NIBS Neuro-Enhancement Protocols in the Elderly

In summary, despite the scarcity of the literature and the heterogeneity of the reports available, a number of promising studies have recorded memory enhancements with the use of NIBS. With regard to the memory paradigms and, stimulation procedures employed and the areas targeted, at least three studies have demonstrated relatively high Hedge's *g* (which was calculated in accordance with the published guidelines (Lakens, 2013) and represents an unbiased method for calculating effect sizes that ultimately relies on the means and the standard deviations) effect sizes (> 0.60) for NIBS stimulation over memory functions (Flöel et al., 2012; Sandrini et al., 2014; Solé-Padullés et al., 2006). In addition, these studies were conducted by independent research teams and included sham groups, randomization procedures, and complete reports of the stimulation effects. Therefore, the common sources of possible bias should be minimal, making the available data more robust.

In terms of the site of stimulation, most of the review studies targeted the PFC, although parietal executive regions have also been successfully stimulated (i.e., Flöel et al., 2012). These studies were either designed or discussed in view of their potential to mediate successful compensatory responses in the aging brain through putative additional frontal lobe activity recruitments. In addition to reflecting the capacity of NIBS to transiently improve memory functions, the studies reviewed should help further our understanding of the neurobiology of current models of cognitive neuroscience of aging. Notably, NIBS allows inference of brain-cognition causality, a property that makes this technique invaluable for testing aging models such as the Hemispheric Asymmetry Reduction in Older Adults (HAROLD; Cabeza, 2002) which initially emerged in the light of correlational evidence deriving from functional imaging studies. The ability of NIBS techniques to causally study neurocognitive models of aging is not limited to memory functions. For instance, the abovementioned study by Meinzer and colleagues (2013) proved that, compared to young individuals, elders showed right frontal lobe over-recruitment during verbal fluency tasks and that anodal tDCS reductions of brain activity in the right medial frontal gyrus were associated with behavioral improvements. This report indicates that in the case of linguistic functions the increase in right frontal lobe areas (leading to a possible "hemispheric reduction asymmetry" pattern compared to young individuals) is not compensatory but rather counter-productive. Other studies oriented toward neuro-enhancement objectives provided valuable information about the neural changes occurring in specific subgroups of elderly participants. In this vein Berryhill and Jones (2012) observed that beneficial effects on WM performance following tDCS were only observed among highly-educated elders. This result, obtained with NIBS research, may shed further light on the "cognitive reserve" hypothesis, since education is the most common proxy used to reflect CR, and since greater cognitive reserve is related to more efficient usage of brain networks in healthy aging (see Bartrés-Faz & Arenaza-Urquijo, 2011 for a review).

While an association between increased excitability and neuro-enhancement is often implicitly assumed, extreme caution should be taken when supposing that increased PFC activity will invariably enhance compensatory mechanisms and improve performance. First, as mentioned above, evidence is now emerging of neural mechanisms underlying the effects of positive stimulation on word generation tasks, in the form of reductions in aberrant hyperactivity both in healthy old adults (Meinzer et al., 2013) and in old adults with MCI (Meinzer, Jähnigen, Copland, et al., 2014). Hence, cognitive enhancement may also be attributed to increased neural efficiency (Kar & Wright, 2014), which may involve a fine-tuning of the neural resources managing inter-network interactions; for instance, facilitating switching between tasks of different levels of difficulty (Meinzer, Lindenberg, Sieg, et al., 2014; Peña-Gómez, Sala-Llonch, et al., 2012). Other explanatory frameworks, such as reduced activity in competitive areas, may also account for the differences in cognition after NIBS (Iuculano & Cohen Kadosh, 2013). Alternatively, improvements caused by NIBS might be driven by conceptually related but non-mutually exclusive cognitive functions in the elderly such as increased inhibitory control, which would highlight the role of top-down processes (Harty et al., 2014).

Overall, the use of NIBS to enhance memory functions in aging appears to be promising. Indeed, robust scientific evidence is accumulating, despite being limited to a small number of studies. As Flöel suggested in relation to neurological conditions (Flöel, 2014) a greater number of multi-center studies using standardized procedures will be needed to facilitate comparison. At the same time, efforts must be made to further understand the biological underpinnings of the cognitive effects of stimulation and to take into account how inter- and intra-individual variability in responses to NIBS influence the results of a given study protocol (see below).

Are NIBS-Induced Memory Enhancements Relevant Outside the Laboratory Setting?

In the previous section, we reviewed studies that used NIBS in order to improve memory processes in healthy elderly individuals, and briefly interpreted the findings. However, statistically significant findings do not necessary translate into clinically significant results. A central question when assessing the ability of NIBS to induce long-term improvements in memory functions in the elderly is whether the benefits obtained persist beyond the treatment itself. Investigations in young individuals (Meinzer, Jähnigen, Copland, et al., 2014; Reis et al., 2009) and patients (Fridriksson, Richardson, Baker, & Rorden, 2011) have demonstrated that the cognitive and behavioral effects of NIBS can last for months. In healthy elderly individuals, most studies have not tested potential longer-term effects, except for the three studies mentioned above (Flöel et al., 2012; Park et al., 2014; Sandrini et al., 2014) which reported memory advantages after stimulation lasting from one week to one month. These results suggest that brain stimulation can modulate long-term memory consolidation processes in the elderly, possibly affecting persistent modifications in synaptic connections (Stagg & Nitsche, 2011).

A relevant factor when considering the potential positive long-term benefits of NIBS effects is whether it should be delivered in single or repeated sessions. It has been proposed that repetitive stimulation may surpass the transient plasticity modulation obtained with isolated sessions, leading to more robust cerebral changes, such as the durable protein synthesis modulations thought to underlie long-term memory gains. Indeed, studies in young volunteers (Meinzer, Jähnigen, Copland, et al., 2014) and elderly participants (Zimerman et al., 2013) have demonstrated more successful learning of motor learning tasks when tDCS was applied during multiple sessions. Prolonged memory benefits (up to 4 weeks) were also observed after tDCS was applied to patients with AD for five consecutive days (Boggio et al., 2012). Given that the use of repeated NIBS sessions is more costly for the clinician, convincing domain-specific evidence is still needed to demonstrate that the potential benefits over single-session NIBS in the elderly are real.

Methodologically, another key question that will need to be addressed is the optimal spacing interval between stimulations. Research into the long-term plasticity phase in animal models has considered brain stimulation training sessions repeated in a relatively tight-spaced period. In parallel, the use of repetitive NIBS sessions in human beings, spaced at intervals of several minutes (i.e., 3–30 min), has obtained greater and more persistent changes in neuroplasticity responses than NIBS applied over more prolonged spacing periods, with the latter appearing to produce more labile and reversible plasticity changes (Goldsworthy, Pitcher, & Ridding, 2014). Therefore, further research should investigate whether frequently applied NIBS sessions result in more durable and stable cognitive benefits than single or more widely spaced sessions.

Another relevant issue regarding the implementation of NIBS is the potential for increased benefits if it is applied concomitantly with cognitive interventions. Cognitive training is emerging as a valid method for the control of age-related cognitive dysfunction (Gates et al., 2013; Kelly et al., 2014). Given that both cognitive training and NIBS can enhance adaptive plasticity mechanisms, one might hypothesize that they may produce synergistic positive effects on cognitive outcomes when applied together (Ditye, Jacobson, Walsh, & Lavidor, 2012). Indeed, among young participants, there is evidence that brain stimulation in combination with cognitive training not only amplifies the benefits of multi-session training regarding the trained task but also improves other conceptually similar untrained cognitive skills (Cappelletti et al., 2013). These results indicate that NIBS may enhance the ecological validity of cognitive training by expanding near transfer effects. The area promises to have many therapeutic applications, and because the limited transfer benefits after cognitive training may be more pronounced in the elderly (Dahlin, Nyberg, Bäckman, & Neely, 2008), it may be particularly interesting for cognitive aging studies. However, while at least three studies have reported the positive adjuvant effects of TMS or tDCS on memory or executive functions in AD (Bentwich et al., 2011; Penolazzi et al., 2014; Rabey et al., 2013), to date only one study (Park et al., 2014) has assessed the combined effect of NIBS with cognitive training in aging. In that study, which involved 10 daily sessions of tDCS and cognitive training, the authors reported that the WM improvements were maintained for up to 28 days after stimulation sessions. However, there was no comparison group (i.e., tDCS without cognitive training), which means that no further conclusions regarding a potential synergistic effect can be drawn. Clearly, future research should address the potential of combining NIBS with cognitive training in memory studies of aging.

The Practical Use of NIBS for the Psychologist: Advantages and Limitations

So far we have highlighted the value of NIBS for the investigation of memory functions in aging, including its potential as a therapeutic tool against age-related cognitive dysfunction. In this section, we discuss some of the more practical issues concerning the versatility and limitations of one technique or procedure over another. The aim is to provide guidance for psychologists aiming to initiate clinical research in this field.

First, most of the studies (see Table 1) to date have used tDCS rather than TMS. At the time of writing, other promising methods with potential for modulating cognitive functions (including memory processes) in human beings such as transcranial random and alternate current stimulation (Garside, Arizpe, Lau, Goh, & Walsh, 2014; Jaušovec & Jaušovec, 2014) are yet to be applied in the cognitive neuroscience of aging. Beyond the scientific issues, this bias (i.e., the use of tDCS rather than TMS) may be related to practical considerations. Despite the fact that both techniques are relatively safe and cause minimal patient discomfort, tDCS is known to have fewer adverse effects than TMS (Bruononi et al., 2011; Fertonani, Ferrari, & Miniussi, 2015; Rossi, Hallett, Rossini, & Pascual-Leone, 2009). Additionally, tDCS is both more portable and cheaper than TMS and requires less technical skill. It can also be more readily coupled with cognitive testing/learning paradigms. TMS is less portable, particularly if neuronavigation is needed to take advantage of its inherently greater spatial (and temporal) resolution. Additionally, tDCS allows for better placebo stimulation (Davis, Gold, Pascual-Leone, & Bracewell, 2013). TMS pulses produce marked somatic sensations that are difficult to emulate in a placebo; in tDCS, on the other hand, it is possible to switch the current off 10–30 s after sensations associated with the onset of tDCS (i.e., itching or tingling) appear that blur the distinction for the participants between sham and placebo procedures. Yet, at high intensity tDCS, this placebo procedure is much less effective, especially when subjects are not naïve to stimulation; this may potentially induce a bias, particularly in crossover studies (Fertonani et al., 2015; O'Connell et al., 2012).

TMS and tDCS can each be applied for long enough to induce brain plasticity responses, and each may enhance the eventual consolidation of long-term memory effects. However, tDCS may again be more suitable for use over relatively extended periods during the learning, consolidation, or retrieval of memory processes, whereas rTMS is usually applied "offline." For ethical and safety issues it should be stressed that, while both techniques have been shown to be safe, guidelines are only available for TMS (Rossi et al., 2009). Importantly, the techniques are not tailored for specific populations such as pediatric or elderly subjects, as they exhibit particular neurodevelopmental, neurophysiological, and molecular characteristics that may have unforeseen interactions with NIBS effects and side effects (Davis, 2014; Sibille, 2013). Thus, the current recommendation is that caution should be taken, particularly if protocols with high frequencies and/or intensities are used. Protocols should include proper training in the basic technical principles of NIBS, its applicability, and ethical and regulatory issues.

An important limitation of the use of NIBS is that significant gaps remain in the mechanistic understanding of the intermediate steps in the cascade of events linking the effects of brain stimulation at a microscopic level with gross changes in behaviour (Bestmann, de Berker, & Bonaiuto, 2015). In the field of cognitive aging, this may even be aggravated by the impact of age on the structure, function, and neurochemical properties of the brain. Knowledge of the basic neurophysiology and cognitive neuroscience of the aging process is not only a basic requirement of further investigation, but will also help with the development of specific hypotheses and with the design of novel stimulation approaches. The aging brain presents highly marked individual differences in terms of atrophy, resilience capacity, and network usage. Although a number of theoretical approaches have been proposed to explain these interindividual differences, the available knowledge of NIBS such as novel methodological approximations and cognitive modeling (Miniussi, Harris, & Ruzzoli, 2013) might allow the refinement of hypotheses and objectives and ultimately optimize the cognitive results achieved with stimulation. In this regard, there is extensive evidence that the effects of NIBS are modulated by several inter- and intra-individual characteristics (Li, Uehara, & Hanakawa, 2015; Maeda, Keenan, Tormos, Topka, & Pascual-Leone, 2000), and that cognitive improvements in one cognitive domain triggered by stimulation may be associated with concomitant interference in other cognitive tasks or measures (Iuculano & Cohen Kadosh, 2013). These aspects should not be seen as limitations of NIBS, but as basic knowledge that will help to define specific methodological procedures in our attempts to target specific regions and determine the optimal parameters for its use. This basic knowledge of the characteristics of the technique, together with theory-based cognitive neuroscience hypotheses of aging, will not only help to predict outcomes, but should ultimately help to optimize the neuro-enhancement properties of brain stimulation in the elderly.

Conclusions

In the present article, we have reviewed the scientific evidence of the ability of NIBS to obtain memory improvements among healthy older adults. We have also described the mechanisms underlying these enhancements proposed in the literature, and have highlighted some approaches that may improve the efficacy of the technique, such as its application across multiple sessions and its concurrent use with learning paradigms or cognitive training strategies.

Overall, the use of NIBS to enhance memory among old adults represents a promising approach for both research and clinical psychology. However, the effects of NIBS are likely to be highly dependent on interindividual differences on specific biomarkers, such as neuroimaging-based measures of brain functional and structural integrity, or the presence of particular genetic variations (i.e., APOE, BDNF). Hence, the abovementioned need for harmonized multicentric protocols should also address the issue of inter- and intra-individual variability as a means to identify individuals who can benefit the most from NIBS interventions.

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